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EXAMINER	
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ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,897	YUN ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,11-28,41,62 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 11-28, 41, 62, 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Supplemental Appeal Brief filed on 6/12/2008, PROSECUTION IS HEREBY REOPENED. New Grounds of Rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Claims 2, 5-10 have been canceled and claim 29-40, 42-61 are withdrawn from consideration. Claims 1, 3, 4, 11-28, 41, 62, 63 are pending and are being examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 11-28, 41, 62, 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. The specification also does not provide support of modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. The specification does not provide adequate description and there are no specific examples to provide support to the claims. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not provide support to the subject matter of administration of a beta blocker to a subject to treat said subject for at least one of the conditions listed in claim 1 wherein said modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and, (8) the quantity of experimentation necessary.

Claims 1, 3, 4, 11-28, 41, 62, 63 are rejected under 35 U.S.C. 112, first paragraph, because the prior art, while being enabling for a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating comprising administering an effective amount of at least one beta blocker to conditions like asthma, hypertension, glaucoma, migraine, anxiety disorders does not reasonably provide enablement for treating all the diseases or disorders listed in claim 1 with all the beta blockers and in combination with all non-beta blocking agents listed in claim 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

(1, 5) The nature of the invention and the breadth of the claims:

The instant claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective

amount of at least one beta-blocker to said subject to treat said subject for at least one of: neurodegenerative conditions; neuroinflammatory conditions; orthopedic inflammatory conditions; lymphoproliferative conditions; autoimmune conditions; inflammatory conditions; infectious diseases, pulmonary conditions; transplant-related conditions, gastrointestinal conditions; endocrine conditions; genitourinary conditions selected from the group of renal failure, hyperreninemia, hepatorenal syndrome and pulmonary renal syndrome; aging associated conditions; neurologic conditions; Th-2 dominant conditions; conditions that cause hypoxia; conditions that cause hypercarbia; conditions that cause hypercapnia; conditions that cause acidosis; conditions that cause academia, pediatric-related conditions; OB-GYN conditions, sudden death syndromes, fibrosis; post-operative recovery conditions; post-procedural recovery conditions; chronic pain; disorders of thermoregulation, cyclic vomiting syndrome and trauma. Claim 21 is limited to few beta blockers, claim 41 to few aging associated conditions. Claims 1, 3, 4, 11-20, 22-28, 62, 63 are very broad with respect to the conditions, number of beta blockers and number of non-beta blocking agents (listed in claim 24).

(3) The relative skill of those in the art:

The relative skill of those in the pharmaceutical and medical arts is high, requiring advanced education and training.

(4) The predictability of the art:

Despite the advance training of those in the art, the art is highly unpredictable. It is still not possible to predict the pharmacological activity or treatment efficacy of a compound based on the structure alone. It is also not possible to predict the efficacy of

a given class of compounds for the treatment of a particular disease absent a mechanistic link between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Typically, in order to verify that a compound will be effective in treating a disease, the compounds must be either tested directly in a patient or in a model that has been established as being predictive of treatment efficacy. In order to predict whether a class of compounds would be effective in treating a disease, the etiology or pathophysiology of the disease must be uncovered, and there should be a nexus between the pharmacological activity of the class of agents and the etiology or pathophysiology of the disease. Absent experimental tests verifying the efficacy of a compound or a strong nexus between the known pharmacological activity of a class of agents and the etiology and/or pathophysiology of the condition, it is impossible to predict whether the compound or class of compounds (here beta blockers) would actually be effective for treating every single condition listed in clam 1. It is impossible to predict that every single beta blocker can be used in combination with every single non-beta blocker class of compounds listed in claim 24. It is impossible to predict that every single beta blocker used in a method of treatment of condition caused by an autonomic nervous system abnormality will be effective in the treatment of every single disorder or disease in the different classes of disorders (that are etiologically different) listed in claim 1. Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Hence it is

highly unpredictable what the outcome would be to due to the interaction of beta blockers with other drugs. Hence there is high unpredictability in the treatment of abnormal autonomic nervous disorders comprising administering a beta blocker with a non beta blocking agent. Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). There is a high degree of unpredictability involved in a method of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to said subject for all the diseases and disorders listed.

(2) The state of the prior art:

Stockley (Are Beta blockers safe?, BMJ, 298, 10 Jun 1989) teaches that two patients developed cardiac failure upon administration of nifedipine (a calcium channel blocker, one of the non beta blockers claimed in claim 24 of the instant application) along with propranolol or atelenol or alprenolol (p 1584, para 2). Chester et al. (Chest 79, 5, May 1981) teaches adverse effects of propranolol on airway function in nonasthmatic chronic obstructive lung disease patients (see Abstract). Houston (Cardiol Clin, 1986, Feb 4(1), 117-35) teaches that several antihypertensive drugs have an adverse effect on glucose tolerance that may partially or completely negate the beneficial effects of reducing blood pressure as it relates to the incidence of coronary heart disease and its complications and beta-blockers without intrinsic sympathomimetic activity have the greatest adverse effect on glucose intolerance. Liebermann et al. (Br J

Obstet Gynaecol, 1978, 678-83, abstract) teaches that beta-adrenergic blockade is harmful to the hypoxic fetus, for these reasons the use of propranolol in hypertensive pregnancies complicated by placental insufficiency may be contraindicated unless there is no satisfactory alternative (See Abstract). Allen et al. teaches that there was an adverse effect of practolol, the occurrence of sinus bradycardia with or without an increase in the frequency of ventricular ectopic beats (See abstract). It has been well known in the prior art that beta blockers are useful in the treatment of angina, heart failure, high blood pressure, glaucoma and various disorders (http://en.wikipedia.org/wiki/Beta_blocker). Salpeter et al. (Cochrane Database of Systemic Reviews, 4, 2002) teach that beta blocker therapy has mortality benefits in patients with hypertension, heart failure, coronary artery disease as well as during the postoperative period (see Abstract). In summary, the guidance from prior art is for the use of beta blockers in conditions like hypertension, heart failure, coronary artery disease as well as during the postoperative period, glaucoma etc, the adverse effects of certain beta blockers and the contraindications of beta blockers in combination with calcium channel blockers. The prior art or the specification does not teach that every single disease or disorder in the different classes of disorders (that are etiologically different) listed in claim 1 will be effectively treated by administration of the beta blockers (known and yet to be discovered) nor does the prior art or specification teach that every combination of beta blocker with a non-beta blocking agent can be used without interactions and be effective in the treatment.

(6, 7) The amount of guidance presented and the presence of working examples:

It has been established that, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839 166 USPQ 18, 24 (CCPA 1970). The specification describes the utility of administration of beta blockers in the subjects and further describes in detail the branches of the autonomous nervous system and the various disease conditions associated in modulating the autonomous nervous system, and the devices and systems for usage in such conditions. The specification does not teach administration of a beta-blocker to a subject to treat such subjects for at least one of the conditions listed in claim 1. The specification also does not provide support of modulating results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. There is no guidance in the specification with respect to the treatment of conditions with high parasympathetic activity with normal sympathetic activity. The specification does not provide specific examples to provide support to the claims. Also, there is a high degree of unpredictability involved in combining a beta blocker with a non-beta blocking drug as there may be drug interactions and if there are any adverse effects such combination may not be workable. In summary, Applicant has provided little guidance beyond what was recognized in the art at the time of filing.

(8) The quantity of experimentation needed:

In order to enable the instantly claimed methods commensurate with the entire scope, a large quantity of experimentation would be necessary. With Applicants' guidance provided in the specification and what is known in the prior art the person of

ordinary skill in the art would have to conduct these experiments administering beta blockers for every single condition listed in claim 1 and with combination of non-beta blockers listed in claim 24. Considering the unpredictability of the combination of compounds due to their drug interactions, this would be an arduous and daunting task. It would require undue experimentation to test each beta blocker for all the conditions listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test each beta blocker with every single non beta blocking agent listed in claim 24 for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. It would require undue experimentation to test all beta blockers for every condition listed in a method of modulating the autonomic nervous system and treating the subjects for those conditions and also to test whether modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention of treating a subject for a condition caused by an autonomic nervous system abnormality comprising modulating at least a portion of said subject's autonomic nervous system by administering an effective amount of at least one beta-blocker to said subject to treat said subject for at least one

of the conditions listed in claim 1. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 14, 19-22, 28, 41, 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March, 1999, p 291-297).

Gambardella et al. teach a method of treating a condition due to deficient parasympathetic activity associated with elevated basal metabolic rate in cancer patients by oral administration of propranolol (see Abstract, p 295, para 1, lines 1-8, p 296, para 4, 1-5). The reference teaches the autonomic nervous system dysfunction in cancer patients with elevated basal metabolic rate, there is an unbalanced sympathetic (SNS)/parasympathetic nervous system (PNS) ratio which may exist due to SNS overactivity in cancer patients due to impaired PNS activity. The reference further teaches that beta-blocker such as propranolol administration may be useful to counteract the negative impact of the SNS on metabolic pathways (p 297, para 3 continued on 298). Hence the reference inherently teaches the sympathetic bias in at least a portion of autonomic nervous system, abnormality characterized by sympathetic

bias, parasympathetic bias with an unbalanced SNS/PNS ratio with high SNS activity and low PNS activity. The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Gambardella et al. teach administration of propranolol 40 mg twice daily (80 mg total) (see Abstract). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Gambardella et al. inherently teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same set of patients with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov 1981, p 938-941).

Brevetti et al. teach an intravenous and oral administration of propranolol for the treatment of Shy-Drager syndrome, a severe degeneration of the autonomic nervous system. The reference further teaches that orthostatic hypotension a condition of Shy-Drager syndrome is mainly dependent on peripheral vasodilation without the normal response of postural vasoconstriction and may be a consequence of an imbalance of alpha and beta adrenoreceptor activity in peripheral nervous system and that beta-blockade may provide an effective means of treating orthostatic hypotension in patients

with Shy-Drager syndrome (p 940 para 2, lines 1-5, continued on page 941). The reference teaches a sympathetic bias and a parasympathetic bias in at least a portion of said autonomic nervous system. The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Brevetti et al. teach administration of propranolol 40 mg three times daily (120 mg total) (p 939, para 1, lines 7-8). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Brevetti et al. inherently teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

Claims 1, 21, 23-25, 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Davies et al. (The J of Intl Med Research, 1988, 16, 173-181).

Davies et al. teach the administration of ibuprofen, a non-steroidal anti-inflammatory drug along with an anti-hypertensive agent and a beta-blocker such as propranolol (see Abstract) to group of patients with hypertension. It is inherent that hypertension, an age-associated condition is common in elderly patients and parasympathetic nerves influence cerebral blood flow during hypertension. The reference does not explicitly teach that modulation of autonomic nervous system results

in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Davies et al teaches administration of propranolol 40-240 mg/day (p 176, Propranolol treatment group). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Davies et al. inherently teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

Claims 1 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Broder et al. (U.S. 6,284,800).

Broder et al. teaches a method of treatment of bronchorestriction in a human or animal, comprising administering an effective amount of a drug selected from the group consisting of D-propranolol (claims 1-3, abstract). The reference teaches administration of 10 mg/kg dosage (A 25 kg patient will be administered an amount of 250 mg) of D-propranolol in a method of treatment of asthma, a pulmonary disorder (col. 12, lines 16-18). The reference does not explicitly teach that modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Broder et al. teaches administration of propranolol 250 mg/day (to a 25 kg patient). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day

taken in, two, three, or four divided doses (para 0091). Hence Broder et al. inherently teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to same subjects with abnormality in autonomic nervous system as claimed in the dosage amount recommended in the specification of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003).

Lampert et al. teaches propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients (see Abstract, p 140, Discussion, para 1). Thus from the teachings of Gambardella et al. and Lampert et al. it is evident that parasympathetic activity is increased after propranolol administration with heart conditions. Lampert et al. teach administration of 180 or 240 mg/day of propranolol (See Methods).

It would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker such as propranolol increases the

parasympathetic activity because of the teachings of Lampert et al. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients. Hence by administration of same drug (as claimed), propranolol to patients would obviously have the same pharmacological effects such as increase in parasympathetic activity. The reference does not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. However, Lampert et al. teach administration of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Lampert et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

Claims 1, 16, 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guilli et al. (Cardiovascular Research, 2001, 208-216) in view of Bugiardini et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90).

Guilli et al. teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (see Abstract).

The reference does not teach administration of a beta blocker in a method of treating a subject to a condition caused by an autonomic nervous system.

Bugiardini et al. teach administration of propranolol to patients with X syndrome and further teach that the average number of ischemic episodes per 24 hours was significantly reduced during propranolol therapy compared with placebo (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a beta blocker such as propranolol in a method of treating a subject to a condition caused by an autonomic nervous system where the abnormality comprises abnormally low parasympathetic activity but normal sympathetic activity such as syndrome X because of the teachings of Bugiardini et al. One having ordinary skill in the art would have been motivated to administer a beta blocker such as propranolol in expectation of reducing the ischemic episodes in patients with syndrome X. The references do not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. However, Bugiardini et al. teach administration of propranolol 120 to 160 mg daily (see abstract). The specification of the instant invention recommends administration of propranolol of about 80 mgs. to about 320 mgs. a day taken in, two, three, or four divided doses (para 0091). Hence Bugiardini et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

Claims 1, 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hill et al. (U.S. 6,449,507) and Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003).

Hill et al. teach the stimulation of nerve or nerve fibers (vagus nerve fibers, hypoglossal nerve fibers, phrenic nerve fibers, parasympathetic nerve fibers, and sympathetic nerve fibers, a vagal nerve) by using electrodes and electrical current and further comprising beta-blockers such as propranolol in a medical procedure such as beating heart surgery, arrythmias, vascular surgery, neurosurgery etc which are aging associated conditions (col. 2, lines 61-65, col. 17, claim 1, claim 10, col. 18, claim 19, co. 20, claim 50). The reference teaches that drugs, drug formulations or compositions suitable for administration to a patient during a medical procedure may include a pharmaceutically acceptable carrier or solution in an appropriate dosage (col. 9, lines 55-59).

Lampert et al.'s teachings discussed as above. Lampert et al. teach that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction patients.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a beta blocker such as propranolol to stimulate a portion of autonomic nervous system because of the teachings of Hill et al. One having ordinary skill in the art at the time of the invention would have been motivated in expectation of success from Hill's teachings. The reference does not explicitly teach that the modulation results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system. Lampert et al. teach administration

of propranolol 180 or 240 mg/day. The specification of the instant invention recommends administration of propranolol of about 80 mg to about 320 mg a day taken in, two, three, or four divided doses (para 0091). Hence Lampert et al. teach the modulation of autonomic nervous system results in substantially equal parasympathetic and sympathetic functions in at least a portion of said autonomic nervous system by administration of the same compound (propranolol) as claimed to patients with abnormality in autonomic nervous system as claimed, in the dosage amount recommended in the specification of the instant application.

Claims 1, 11, 13 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garrett et al. (Quarterly J of Expt. Physiology, 1987, 72, 357-68).

Garrett et al. teach administration of a beta blocker such as propranolol 1mg/kg (calculates to 70 mg for a 70 kg patient) to modulate autonomic nervous system in salivary glands. The reference teaches that parasympathetic and sympathetic systems can be stimulated by administration of a beta blocker such as propranolol. The reference teaches high parasympathetic stimulation and partial and complete inhibition of secretion of kallikrein by administration of propranolol followed by hydroergotamine (an alpha blocker). The reference teaches the modulation of parasympathetic and sympathetic activities and thus teaches the high parasympathetic and normal sympathetic condition at one stage of modulation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer a beta blocker such as propranolol in a method of treating a subject to a condition caused by an abnormality of autonomic nervous system wherein

the abnormality comprises high parasympathetic activity and normal sympathetic activity from Garett et al.'s teachings. The reference teaches that parasympathetic and sympathetic systems can be stimulated by administration of a beta blocker such as propranolol. The reference further teaches the inhibition of secretion of kallikrein by administration of propranolol followed by hydroergotamine (an alpha blocker). Hence by modulating the autonomic nervous system Garrett et al. teaches the system with a high parasympathetic activity and a normal sympathetic activity.

Response to Arguments

Applicant's arguments with respect to the rejections of the claims have been fully considered but are moot in view of the new grounds of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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